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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* BASKARAN CHANDRASEKAR and
JEAN-FRANCOIS TANGUAY,
Appellants[1]

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Appeal 2009-014308
Application 10/088,405
Technology Center 1600

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Decided: March 17, 2010

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Before CAROL A. SPIEGEL, RICHARD M. LEBOVITZ, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The real party-in-interest is the INSTITUT DE CARDIOLOGIE DE MONTRÉAL (Appellants' Brief on Appeal Pursuant to 37 C.F.R. § 41.37, filed 5 June 2008 (hereinafter "Br."), at 1).

Appellants appeal under 35 U.S.C. § 134 from the Examiner's final rejection of all pending claims, claims 1, 3-8, 10-14, 16-18, and 20-24 (Br. 2; Ans.[2] 2). We have jurisdiction under 35 U.S.C. § 134. We AFFIRM.

INTRODUCTION

The subject matter on appeal is directed to a method comprising administering 1 to 5,000 µg/kg body weight (e.g., 73 to 363,636 µg/160 lbs body weight) of 17ß estradiol to a site of vascular injury in the lumen of a blood vessel of a patient to improve the outcome of a coronary angioplasty. Angioplasty is used to widen a narrowed or obstructed blood vessel by inserting a balloon catheter, for example, into the vessel and mechanically inflating the balloon to dilate the inside (lumen or channel) of the vessel. However, the catheter may scrape away the inside layer(s) of the blood vessel wall and may tear the vessel's wall during its insertion, thereby causing a vascular injury. (The innermost layer of a blood vessel is called the endothelium and its cells (endothelial cells) form an interface between the circulating blood in the lumen and the rest of the blood vessel wall. Beneath the endothelium is a layer of subendothelial connective tissue, followed by a layer of smooth muscle cells, and finally another layer of connective tissue called the adventitia.) The vascular injury may lead to a re-obstruction of the blood vessel (restenosis). (*See generally*, Spec.[3] 1:9-14 and 2:21-24; Ungs[4] 1:12-16; Stack Decl.[5] ¶¶ 3-4, 6-7.)

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[2] Examiner's Answer mailed 21 August 2008 (hereinafter "Ans.").
[3] Specification of application 10/088,405 (hereinafter "Spec.").
[4] U.S. Patent 5,866,561, *Local Delivery of Estrogen for Angiogenesis*, issued 2 February 1999, to Mark T. Ungs, (hereinafter "Ungs") (Br. Exh. 2).
[5] Declaration of Richard Sean Stack, M.D., FACC, dated 25 July 2005 (hereinafter "Stack Decl.") (Br. Exh. 1).

Claim 1 is illustrative and reads (Br. Claims App. 20):

> 1. A method of improving reendothelization and vascular endothelial function in a patient in need of such improvement, which comprises administering to said patient 17-ß estradiol or a derivative thereof, in an amount effective to improve reendothelization and vascular endothelial function with a device at an injured site in the lumen of a blood vessel having suffered vascular injury, wherein the 17-ß estradiol or a derivative thereof is present in a dose unit of 1 to 5000 µg/Kg of patient's body weight.

Claim 5 requires that the 17ß estradiol or derivative be present in a pharmaceutically acceptable carrier comprising hydroxypropyl-beta-cyclodextrin (hereinafter "HPCD"). Claim 7 requires that the 17ß estradiol or derivative be admixed with a carrier comprising at least 0.63 mg HPCD per kilogram of patient body weight. Claims 12 and 13 require that the 17ß estradiol or derivative be administered following or simultaneously with a percutaneous transluminal coronary angioplasty (hereinafter "PTCA"), respectively.

The Examiner has rejected the claims as unpatentable as follows:[6]

I. claims 1, 3, 4, 8, 10, 12-14, 16-18, 20, and 22-24 under 35 U.S.C. § 103(a) over the combined teachings of Ungs, O'Brien,[7] and Bauters[8] (Ans. 3-9),

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[6] The Examiner withdrew the final rejection of claim 24 under 35 U.S.C. § 112, second paragraph (Ans. 18-19).

[7] Jeanne E. O'Brien et al., *Relation Between Estrogen Replacement Therapy and Restenosis After Percutaneous Coronary Interventions*, 28 JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 1111-18 (1996) (hereinafter "O'Brien") (Br. Exh. 3).

II. claims 5-7, 11, and 21 under 35 U.S.C. § 103(a) over the combined teachings of Ung, O'Brien, Bauters, and Pitha[9] (Ans. 9-11),

III. claims 1, 3, 4, 8, 10-14, 16-18, and 20-24 under 35 U.S.C. § 103(a) over the combined teachings of Ungs, Fontana,[10] and Grainger[11] (Ans. 11-16), and

IV. claims 5-7 under 35 U.S.C. § 103(a) over the combined teachings of Ungs, Fontana, Grainger, and Pitha (Ans. 16-18).

REJECTIONS I AND II

The Examiner's findings and conclusions

As to rejection I, the Examiner found that Ungs teaches that restenosis is a significant problem following PTCA and that increasing blood flow near a stenosed region is desirable in place of or in addition to PTCA (Ans. 4). The Examiner also found that Ungs teaches administering 17ß estradiol to the lumen of a blood vessel having suffered a vascular injury using a drug delivery balloon catheter or a coated stent to induce angiogenesis (growth of new blood vessels from existing blood vessels) near a site of stenosis (*id.*). According to the Examiner, Ungs does not expressly teach administering 17ß

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[8] Christophe Bauters and Jeffrey M. Isner, *The Biology of Restenosis*, 40 PROGRESS IN CARDIOVASCULAR DISEASES, 107-16 (1997) (hereinafter "Bauters") (Br. Exh. 4).

[9] U.S. Patent 4,727,064, *Pharmaceutical Preparations Containing Cyclodextrin Derivatives*, issued 23 February 1988, to Josef Pitha (hereinafter "Pitha") (Br. Exh. 5).

[10] U.S. Patent 5,384,332, *Methods for Inhibiting Aortal Smooth Muscle Cell Proliferation and Restenosis with 1,1,2-Triphenylbut-1-ene Derivatives*, issued 24 January 1995 to Steven A. Fontana (hereinafter "Fontana") (Br. Exh. 6).

[11] U.S. Patent 6,117,911, *Compounds and Therapies for the Prevention of Vascular and Non-Vascular Pathologies*, issued 12 September 2000, to David J. Grainger et al. (hereinafter "Grainger") (Br. Exh. 7).

estradiol in the recited dosage range or for the recited purpose of improving reendothelization and vascular endothelial function (*id.* at 5). However, according to the Examiner, since

> Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

(Ans. 7-8.)

The Examiner further found that O'Brien teaches that estrogen replacement therapy, with 17ß estradiol for example, reduces restenosis, especially in patients having atherectomies, and has been associated with improved endothelial function (*id.* at 5-6). The Examiner found that Bauters teaches that dysfunctional regenerating endothelium may contribute to thickening of the innermost layer of a blood vessel due to smooth muscle cell (hereinafter "SMC") proliferation since the endothelium appears to modulate the proliferative activity of underlying SMCs (*id.* at 6). In particular, the Examiner found that O'Brien teaches that physiologic levels of estrogen inhibit proliferation of vascular smooth muscle from the coronary arteries of female pigs (*id.* at 20-21).

The Examiner concluded that it would have been obvious to treat a patient with 17ß estradiol or a derivative thereof to improve reendothelization and vascular endothelial function because (i) Ungs and O'Brien teach that estrogens, including 17ß estradiol, reduce restenosis, (ii) O'Brien teaches that inhibiting SMC proliferation reduces restenosis and that

estrogen replacement therapy improves endothelial function, and (iii) Bauters teaches that SMC proliferation is related to dysfunctional regenerating endothelium (vascular endothelial dysfunction) (*id.* at 7, 20-22). The Examiner further concluded that it would have been a matter of routine optimization to administer 17ß estradiol or a derivative thereof in the claimed dosage range (Ans. 8, 23).

As to rejection II, the Examiner found that none of Ungs, O'Brien, and Bauters teach administering 17ß estradiol in a pharmaceutically acceptable carrier comprising HPCD. The Examiner found that Pitha teaches that providing 17ß estradiol in combination with a pharmaceutically acceptable carrier including HPCD improves the solubility and absorption of the 17ß estradiol (*id.* at 10). The Examiner concluded that it would have been obvious to administer 17ß estradiol in an HPCD containing pharmaceutically acceptable carrier with an expectation of improving the solubility of 17ß estradiol in the drug delivery device/route of administration and thereby increasing the absorption of the 17ß estradiol by the patient as disclosed and/or suggested by Pitha (*id.* at 11, 23-24). The Examiner further concluded that it would have been obvious and within ordinary skill in the art to optimize the amount of HPCD provided in the administered dosage (*id.* 10-11).

Appellants' position

As to rejection I, Appellants argue that Ungs' statement that "Administration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis" at column 1, lines 49-51, misinterprets two references discussed earlier in that paragraph,

which teach *systemic* administration of therapeutic agents, i.e., Hughes[12] and Javitt[13] (Br. 5-7). Specifically, Appellants assert that Hughes teaches daily oral administration of estrogen and phytoestrogen to decrease osteoporosis- and coronary heart disease-related morbidity and mortality in postmenopausal women, while Javitt teaches oral administration of 27-hydroxycholesterol or related compound or a sterol 27-hydrolase stimulant to prevent or treat restenosis (*id.* at 6-7). Further according to Appellants, Ungs teaches away from the claimed invention by suggesting that estrogen-induced angiogenesis could replace PTCA (*id.* at 7).

Appellants contend that O'Brien admits that there have been conflicting reports regarding the effect of estrogen on the proliferation of SMCs and, in any event, that the present claims recite a method of improving regeneration of the endothelium and its vascular function, not a method of inhibiting SMC proliferation (*id.* at 8). Relying on the testimony of Dr. Stack, Appellants argue that one cannot predict whether an agent that prevents or reduces SMC proliferation and/or vessel wall thickening will also prevent promote regeneration of the endothelium (*id.*). Thus, Appellants maintain that O'Brien fails to teach or suggest the claimed invention (*id.* at 8-9) or to provide a reasonable expectation of success of improving reendothelization and vascular endothelial function by administering 17ß estradiol as claimed (*id.* at 10-11).

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[12] U.S. Patent 5,516,528, *Dietary Phytoestrogen in Estrogen Replacement Therapy*, issued 14 May 1996, to Claude L. Hughes et al. (hereinafter "Hughes") (Br. Exh. 8).

[13] U.S. Patent 5,376,652, *Administration of a 27-Hydroxycholesterol or Related Compound or Sterol-27-Hydroxylase Stimulant to Prevent Restenosis Following Vascular Endothelial Injury*, issued 27 December 1994, to Norman B. Javitt (hereinafter "Javitt") (Br. Exh. 9).

Appellants also contend that Bauters teaches that a combination of factors, including SMC proliferation, elaboration of extracellular matrix, thrombosis, and vascular remodeling, causes restenosis and that the contribution of each factor varies from one patient to another and even from one lesion to another in the same patient, e.g., endothelial cells *may* maintain SMC quiescence and a dysfunctional regenerating endothelium *may* contribute to thickening of the lining of a blood vessel because of reduced inhibition of platelet aggregation and SMC proliferation (Br. 9). According to Appellants, Bauters only suggests that it would have been "obvious to try" to vary each of the contributory factors until arriving at a successful result (*id.* at 9-11).

Appellants further contend that none of Ungs, O'Brien and Bauters discloses or suggests administering 17ß estradiol or a derivative in a dose of 1 to 5,000 µg/kg body weight (*id.* at 11-14). Appellants also contend that the Examiner's statement that Ungs' method would necessarily also improve reendothelization and vascular endothelial function is unsupported speculation (*id.* at 12-13).

As to rejection II, Appellants argue that Pitha does not remedy the deficiencies of Ungs, O'Brien, and Bauters (*id.* at 15). In addition, Appellants argue that Pitha discusses solubilizing estradiol in HPCD in the context of topical, parenteral, oral or buccal preparations and not in the context of a device, e.g., a stent, and thus there is no motivation to combine Pitha with Ungs, O'Brien, and Bauters (*id.*).

Issues

At issue is whether

(i) Ungs teaches administration of estrogen to the stenosed, dilated region after PTCA to prevent restenosis;

(ii) Ungs teaches away from the claimed invention by suggesting that estrogen-induced angiogenesis could replace PTCA;

(iii) Ungs' method of estrogen-induced angiogenesis inherently improves reendolization and vascular endothelial function as claimed;

(iv) the combined teachings of Ungs, O'Brien, and Bauters would have motivated one of ordinary skill in the art to administer 1 to 5,000 µg 17ß estradiol or a derivative thereof/kg subject body weight with a device to a site of vascular injury in the lumen of a blood vessel of the subject with a reasonable expectation of preventing restenosis; and,

(v) it would have been obvious to locally administer 17ß estradiol in an HPCD containing pharmaceutically acceptable carrier as taught by Pitha using a drug delivery catheter or stent as taught by Ungs with a reasonable expectation of success and, if so, in the amount of at least 0.63 mg HPCD/kg body weight as recited in claim 7.

Findings of Fact

The following findings of fact (hereinafter "FF") are supported by a preponderance of the evidence of record.

A. Ungs

[1] According to Ungs, PTCA is used to treat patients with coronary heart disease (Ungs 1:12-14).

[2] Restenosis following PTCA is a significant problem (Ungs 1:17-18).

[3] Various treatments have been suggested to treat restenosis, including applying smooth muscle cell (SMC) anti-proliferation agents (Ungs 1:21-39), e.g., "Woods . . . discloses an application of . . . estrogen . . .

to inhibit restenosis" (*id.* 1:24-27) and "administration of an effective amount of Transforming Growth Factor-beta activators or production stimulators . . . has also been proposed by Grainger . . . " (*id.* 1:34-39).

[4] Ungs states that

> [i]t is believed that the more common occurrence of restenosis in men compared to women suggests [that] hormones play a role. Oral, transdermal, and implant delivery administration of a therapeutically effective amount of estrogen has been suggested as a method for reducing the risk of heart disease by Hughes . . . . A method for reducing restenosis by administering estrogen in a dose sufficient to stimulate synthesis of 27-hydroxychloresterol in the vascular endothelium tissue has also been proposed by Javitt . . . . *Administration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis*

(Ungs 1:40-51, emphasis added).

[5] According to Ungs,

> PTCA is not always a successful solution or even a viable treatment option, as not all stenosed regions can be treated with PTCA. For example, some regions are unreachable with the required size high pressure balloon, which must be advanced through the narrowed, occluded vessel region. Some stenoses are totally blocked, denying entry to a dilatation catheter attempting to advance within. Other vessel regions are too narrow or geometrically too tortuous for dilitation. Damage to weakened vessel walls is a possibility during balloon inflation as well, and may preclude PTCA in some cases. Treatment to increase perfusion to heart tissue, in place of, or in addition to, PTCA would be desirable.

(Ungs 1:52-63).

[6] Thus, Ungs states that "[t]he present invention provides a method for increasing circulation [perfusing] heart tissue involving the application of estrogen compounds to blood vessel walls to promote angiogenesis" (Ungs 1:66-2:2).

[7] The estrogen, preferably 17ß estradiol or estriol, is locally applied proximal to, or upstream of, ischemic tissue or stenosis in an effective amount for causing angiogenesis; in one method, a double walled drug delivery balloon catheter is used, e.g., to hold the estrogen in place against the vessel, promoting absorption through the vessel wall, while allowing blood to flow through the blood vessel (Ungs 2:6-25, 2:60-3:14; 4:10-11; claim 1).

B. O'Brien

[8] According to O'Brien, "estrogen replacement therapy in women has been associated with a reduction in cardiovascular events and improvement in endothelial function" (O'Brien 1111, abstract "Background").

[9] Further according to O'Brien, "recent studies . . . suggest that estrogen may reduce the progression of existing coronary artery disease in postmenopausal women, favorably modulate the vascular biology of atherosclerotic coronary arteries and limit the proliferation of vascular smooth muscle after endothelial injury" (O'Brien 1111, ¶ 2).

[10] O'Brien studied the relationship between estrogen replacement therapy, including estradiol regimens, and the rate of restenosis after coronary angioplasty and atherectomy (O'Brien abstract; 1113, ¶ 2).

[11] According to O'Brien, while there have been conflicting reports, the majority of the studies to date in animal models reported that estrogen

significantly inhibited neointimal proliferation after arterial balloon injury (O'Brien 1116, ¶ 1).

[12] O'Brien concluded that her exploratory study, "the first to clinically evaluate the effect of estrogen replacement therapy on restenosis in humans" (O'Brien 1116, ¶ 1)

> suggests that estrogen replacement therapy in postmenopausal women may reduce restenosis after coronary intervention, particularly in patients receiving directional coronary atherectomy. Given the potential clinical importance of these findings, the use of estrogen replacement therapy as a means of preventing restenosis after coronary intervention deserves further evaluation.

(O'Brien 1117, ¶ 4.)

C. Bauters

[13] According to Bauters, "[t]he healing response after arterial injury . . . begins immediately after the initial injury . . . This 'growth response' that leads to the development of a neointimal thickening, also known as neointimal hyperplasia, involves three key elements: smooth muscle cells (SCMs), endothelial cells, and the extracellular matrix" (Bauters 107, ¶ 3).

[14] SCM activation after arterial injury leads to proliferation, migration, and synthesis of extracellular matrix (Bauters 107, ¶ 4; 108, ¶ 2).

[15] Bauters discloses that neointimal thickness is closely related to the presence of a regenerated endothelium and that intimal areas which are rapidly covered by a continuous endothelium are protected from the accumulation of intimal SCMs (Bauters 108, ¶ 6).

[16] Specifically, a dysfunctional regenerating endothelium may contribute to development of a thickened intima because of reduced inhibition of platelet aggregation as well as SMC proliferation (Bauters 109, ¶1).

D. Pitha

[17] Pitha teaches improving the dissolution properties of 17ß estradiol and, hence, its absorption by the body, by solubilizing the 17ß estradiol in aqueous solutions of HPCD (Pitha 1:8-15; Table 1; 5:29-34; Table 2).

E. Hughes

[18] According to Hughes, administration of a composition comprising about 1-2 mg mammalian estrogen and about 25-100 mg phytoestrogen to postmenopausal women on a daily basis will decrease their risk of osteoporosis and coronary heart disease (Hughes 5:59-63).

[19] Preferably, the estrogen is estradiol and the phytoestrogen is an isoflavine such as genistein or daidzein (Hughes 1:55-59).

[20] The composition may be delivered orally or by transdermal or implant delivery systems (Hughes 1:46-47, 50-53).

F. Javitt

[21] Javitt discloses a method of reducing the occurrence of restenosis following injury to the lumen of a blood vessel resulting from a mechanically widening, e.g., after angioplasty, by administering a 27-hydroxycholesterol or related compound orally or, preferably, intravenously in an aqueous solution of HBCD (Javitt 2:64-3:9).

[22] Alternatively, Javitt discloses administering a sterol 27-hydroxylase stimulant to increase the synthesis of, and thereby provide, 27-hydroxycholesterol in the vascular tissue (Javitt 3:10-15).

G. Stack Declaration

[23] Richard Sean Stack, M.D., FACC, testifying for Appellants as an expert in the field of angioplasty and restenosis, explained that during angioplasty insertion of the device used to increase a blood vessel's interior channel (lumen) may injure the blood vessel (Stack Decl. ¶¶ 1, 2, 6).

[24] According to Dr. Stack, this injury may lead to a re-obstruction or restenosis of the blood vessel channel as result of a number of events, including pathological proliferation and migration of SMCs which cause a thickening of the blood vessel wall (Stack Decl. ¶ 7).

[25] Dr. Stack testified that it is useful to inhibit SMC proliferation and, more recently, to promote vessel repair, specifically, to regenerate the inner lining of the blood vessel, i.e., its endothelium (a process called reendothelization), and consequently restore endothelial function, in order to prevent restenosis, by using certain anti-restenosis agents (Stack Decl. ¶¶ 3, 8, 9, 10).

[26] According to Dr. Stack, most anti-restenosis agents are anti-SMC proliferative agents (Stack Decl. ¶ 10), but very few agents are known to promote blood vessel wall repair (*id.*, ¶ 11).

[27] Dr. Stack testified that, in his experience, whether an anti-SMC proliferation and/or anti-blood vessel wall thickening agent will also promote reendothelization cannot be predicted (Stack Decl. ¶ 12).

[28] Dr. Stack cited paclitaxel and sirolimus as known anti-proliferative agents which do not also improve reendothelization (Stack Decl. ¶ 13).

[29] Dr. Stack concluded that, in his opinion, "the knowledge that beta-estradiol had an ability to reduce smooth muscle cell proliferation was

not sufficient, for someone skilled in the art, to predict that beta-estradiol could also promote reendothelization and endothelial function" (Stack Decl. ¶ 14).

Other findings of fact follow below.

Legal principles

A claimed invention is not patentable if its subject matter would have been obvious to a person of ordinary skill in the art. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 400 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 3 (1966). The prior art need not disclose the same purpose for a claimed method in order to establish its obviousness under 35 U.S.C. § 103. *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990). All that is necessary is that one of ordinary skill in the art would have had some reason for performing the claimed method step. *In re Kemps,* 97 F.3d 1427, 1430 (Fed. Cir. 1996). Moreover, "[i]t is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (affirming a rejection under 35 U.S.C. § 103).

It is also well settled that a determination of inherency cannot be established by probabilities or possibilities, and that it is incumbent upon the Examiner to establish the inevitability of the inherence based upon factual evidence or persuasive scientific reasoning. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981); *In re Wilding*, 535 F.2d 631, 635-36 (CCPA 1976). "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) (affirmed a rejection under 35 U.S.C. § 103 based in part on

inherent disclosure of one of the references). *See also In re Grasselli*, 713 F.2d 731, 739 (Fed. Cir. 1983).

Furthermore, "a reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985) and "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art" *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

However, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008) (quoting *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006)).

Analysis

First, as noted by the Examiner (Ans. 19), Ungs and Javitt identify a specific site of injury to be treated, i.e., blood vessels injured by PTCA, in order to prevent restenosis from occurring (FF 5, 21). According to Ungs, various treatments had been suggested by others to treat restenosis, including "application of smooth muscle cell anti-proliferation agents, including estrogen" (FF 3). Ungs notes an association between reduced restenosis in men versus women which is consistent with Hughes' teaching that women taking estrogen replacement therapy (postmenopausal women) have a reduced risk of heart disease (FF 4, 18).

In particular, Ungs expressly states "Administration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis" (FF 4). Moreover, Ungs not only

suggests that it would be desirable to increase perfusion to heart tissue in addition to PTCA (FF 5), but also expressly applies estrogen compounds to blood vessel walls to promote angiogenesis (FF 6-7), thereby increasing perfusion to heart tissue.

Appellants essentially argue that systemic administration of estrogen does not suggest localized administration of estrogen to treat or prevent restenosis. We disagree. Appellants have not explained why, for example, one of ordinary skill in the art would have *systemically* administered female hormones to a male patient undergoing PTCA to prevent or treat restenosis instead of confining delivery of female hormones to the site of injury. In addition, as noted by Appellants (Br. 6), Hughes teaches oral, transdermal and *implant* delivery of estrogen containing compositions (FF 18, 20). Appellants have not argued that an implant is not a device or that one of ordinary skill in the art would have been incapable of using a drug delivery device to implant a drug in a particular site in the body. Indeed, Ungs' use of a double walled drug delivery balloon catheter suggests that localized drug delivery to a targeted site in a blood vessel is within ordinary skill in the art (FF 7). Therefore, we agree with the Examiner that administration of estrogen to the stenosed, dilated region after PTCA for the purpose of treating or preventing restenosis is fairly suggested by Ungs (Ans. 19).

Second, Appellants' argument that Ungs teaches away from the claimed invention is based on a selective, incomplete reading of Ungs. As noted by the Examiner (*id.*), Ungs teaches applying estrogen to blood vessels to promote angiogenesis as an alternative or *additional treatment to PTCA* in order to increase circulation to the heart (FF 6). Thus, Ungs does not clearly teach away from the claimed invention.

Third, we find that the Examiner has established a prima facie case of inherency with respect to improving reendothelization and endothelial function as claimed. The Examiner's rationale is quite reasonable inasmuch as Ungs teaches administering the same compound via the same method as claimed to achieve the same generic purpose of reducing the incidence of restenosis following a treatment that induces vascular injury, e.g., PTCA. It is well settled that when a claimed product or process reasonably appears to be substantially the same as a product or process disclosed by the prior art, the burden is properly upon the applicant to demonstrate that the prior art product or process does not necessarily or inherently possess characteristics attributed to the claimed product or process. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Thus, the burden has shifted to Appellants to establish that the effective amount of estrogen, preferably 17ß estradiol, administered in Ungs' method is outside of the claimed dosage range. This Appellants have not done.

Fourth, regarding the alleged lack of motivation to combine the references and a lack of a reasonable expectation of success in doing so, O'Brien expressly teaches that estrogen replacement therapy in women has been associated with improvement in endothelial function (FF 8) and expressly suggests that estrogen may favorably modulate the vascular biology of atherosclerotic coronary arteries (FF 9). According to O'Brien, her own studies in human were consistent with using estrogen replacement therapy as a means of preventing restenosis after coronary intervention (FF 12). In the Examiner's words, "O'Brien . . . establish[es] that estrogen can reduce restenosis[] and improve endothelial function by inhibiting SMCs" (Ans. 21). Furthermore, Bauters discloses that intimal areas which are

rapidly covered by a continuous endothelium (reendothelized) are protected from accumulating SMCs (FF 15), i.e., a dysfunctional regenerating endothelium may contribute to neointimal thickening because of its reduced ability to inhibit SMC proliferation (FF 16). Thus, it would have been obvious to apply an estrogen, e.g., 17ß estradiol, proximal to, or upstream of, ischemic tissue or stenosis using a double walled drug delivery balloon catheter as taught by Ungs to allow the estrogen to be absorbed through the vessel wall in an amount consistent with that provided by estrogen replacement therapy (a physiologic amount), with a reasonable expectation of improving endothelial function as expressly taught by O'Brien and of preventing restenosis by inhibiting SMC proliferation as taught and/or suggested by O'Brien and Bauters and/or by helping regenerate a functional endothelium as suggested by Bauters.

Indeed, such a reasonable expectation of success is consistent with Dr. Stack's testimony that it is useful to inhibit SMC proliferation and to regenerate the inner lining of the blood vessel after injury caused by an angioplasty in order to prevent restenosis (FF 23-25). We are mindful of Dr. Stack's testimony that, in his experience, it is unpredictable whether an anti-SMC proliferation agent will also promote reendothelization (FF 27). However, Dr. Stack testified that using reendothelization to prevent restenosis is a more recent technique (FF 25) and did not testify regarding estrogen therapy and its use in preventing restenosis, inhibiting SMC proliferation, and improving endothelial function as disclosed by O'Brien and Bauters. Since Dr. Stack did not testify regarding the closest prior art, we weigh his testimony accordingly.

Thus, we agree with the Examiner that the combined teachings of Ungs, O'Brien, and Bauters would have motivated one of ordinary skill in the art to administer an estrogen such as 17ß estradiol with a device to a site of vascular injury in the lumen of a blood vessel of a patient with a reasonable expectation of preventing restenosis. We also agree with the Examiner that the claimed dosage of 1 to 5,000 µg 17ß estradiol (estrogen)/kg body weight would have been a matter of routine optimization given the direction of O'Brien regarding estrogen replacement therapy and the directions of Ungs, O'Brien, and Bauters to administer sufficient estrogen, e.g., 17ß estradiol, to prevent restenosis. We note that Appellants have not proffered evidence of unexpected results based on the claimed dosage range or substantively challenged the Examiner's reason for administering estrogen, i.e., to prevent restenosis by inhibiting SMC proliferation.

Fifth, as noted by the Examiner (Ans. 24), 17ß-estradiol must first be solubilized before being administered. Pitha expressly teaches that an aqueous carrier containing HPCD improves the solubility of 17ß-estradiol therein and, thereby, its absorption by the body (FF 17). Therefore, it would have been obvious to use 17ß estradiol dissolved in a pharmaceutically acceptable aqueous carrier containing HPCD in the method of Ungs/O'Brien/Bauters with a reasonable expectation of improving its absorption by the body as taught by Pitha. Moreover, it would have been a matter of routine experimentation to optimize the amount of HPCD used to solubilize the 17ß estradiol in view of Pitha's teachings. We also note that Appellants have not proffered evidence of unexpected results based on the claimed dosage range.

Conclusion

Therefore, based on the foregoing, we sustain the rejections of claims 1, 3, 4, 8, 10, 12-14, 16-18, 20, and 22-24 under § 103 over the combined teachings of Ungs, O'Brien, and Bauters; and, of claims 5-7, 11, and 21 under § 103 over the combined teachings of Ungs, O'Brien, Bauters, and Pitha.

Ungs teaches administration of estrogen to the stenosed, dilated region after PTCA for the purpose of preventing restenosis.

Ungs does not teach away from the claimed invention because Ungs suggests that estrogen-induced angiogenesis be used in addition to PTCA.

It reasonably appears that Ungs' method of estrogen-induced angiogenesis inherently improves reendolization and vascular endothelial function as claimed.

The combined teachings of Ungs, O'Brien, and Bauters would have motivated one of ordinary skill in the art to administer 1 to 5,000 µg 17ß estradiol or a derivative thereof/kg subject body weight with a device to a site of vascular injury in the lumen of a blood vessel of the subject with a reasonable expectation of preventing restenosis.

It would have been obvious to locally administer 17ß estradiol in an HPCD containing pharmaceutically acceptable carrier as taught by Pitha in order to improve its solubility in the carrier and, thereby, its absorption by the body, with the claimed amount of HPCD in the 17ß estradiol carrier being a matter of routine optimization.

REJECTIONS III and IV

The Examiner's findings and conclusions

As to rejection III, the findings of the Examiner regarding the teachings of Ungs have been discussed above. The Examiner further found that Fontana teaches administering 17ß estradiol derivatives in an amount from 0.1% to 99.9% by weight of the formulation to inhibit restenosis and aortal SMC proliferation (Ans. 12-13, 15). The Examiner also found that Grainger teaches administering compounds to treat vascular traumas, including restenosis following angioplasty (*id.* at 13). In particular, the Examiner found that Grainger teaches that the compound is an inhibitor of SMC proliferation and inhibition of SMC can allow more rapid and complete reendothelization (*id.*). The Examiner concluded that the claimed method would have been obvious in view of Ungs' teaching that 17ß estradiol reduces restenosis, Fontana's teaching that estrogen derivatives reduce restenosis and inhibits aortal SMC proliferation, and Grainger's teaching that connects restenosis, SMC proliferation, and improved reendothelization and vascular endothelial function (Ans. 14).

As to rejection IV, the Examiner again relies on Pitha's teaching that providing 17ß estradiol in combination with a pharmaceutically acceptable carrier including HPCD improves the solubility and absorption of the 17ß estradiol (*id.* at 17). The Examiner again concluded that it would have been obvious to provide the HPCD containing pharmaceutically acceptable carrier of Pitha in the 17ß estradiol drug delivery method of Ungs/Fontana/Grainger with an expectation of improving the solubility and absorption of the 17ß estradiol compound to a subject (*id.* at 18).

Appellants' position

As to rejection III, Appellants argue, in relevant part, that neither Fontana nor Grainger teach administration of 17ß estradiol or a derivative thereof and, therefore, do not remedy the deficiencies of Ungs (Br. 15-17).

As to rejection IV, Appellants argue, in relevant part, that Pitha does not remedy the deficiencies of Ungs, Fontana, and Grainger.

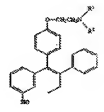
Issue

The dispositive issue is whether Fontana and/or Grainger teach or suggest administering 17ß estradiol or a derivative thereof to reduce or prevent restensosis.

Additional Findings of Fact

H. Fontana

[30] Fontana describes a group of 1,1,2-triphenylbut-1-ene derivatives of formula I, i.e.,



where $R^1$ and $R^2$ may be the same or different, provided that when $R^1$ and $R^2$ are the same, each is a methyl or ethyl group, and when $R^1$ and $R^2$ are different, one of them is a methyl or ethyl group and the other is a benzyl group, or a pharmaceutically acceptable salt thereof, that are useful for inhibiting aortal SMC proliferation, particularly restenosis, in humans (Fontana 1:8-12; 2:41-3:24).

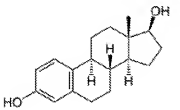
I. Grainger

[31] According to Grainger, TGFß may inhibit the proliferation and migration of SMCs after vascular injury (Grainger 1:17-18).

[32] Grainger describes a method of preventing diminishment of blood vessel lumen associated with vascular trauma by administering one or more agents effective to elevate the levels of TGFß, preferably aspirinates, such as copper 2-acetylsalicylate or copper 2-hydroxybenzoate (Grainger 1:45-50; 2:25-45).

J. Structure of 17ß estradiol

[33] The chemical structure of 17ß estradiol is




(*see e.g.,* Wikipedia[14]).

Analysis

The Examiner's conclusion of obviousness is based on the finding that Fontana teaches using an estradiol derivative to inhibit aortal SMC proliferation and restenosis (Ans. 24 and 25-26). However, as pointed out by Appellants (Br. 15-17), neither Fontana nor Grainger teach administering estrogens or derivatives, much less 17ß estradiol or a derivative thereof (compare FF 30, 32, 33). Since the Examiner's conclusion of obviousness is based on an incorrect factual finding, we reverse the rejections based on the combined teachings of Ungs, Fontana, and Grainger alone or further in view of Pitha.

Conclusion

[14] "Estradiol" – Wikipedia downloaded 2 March 2010 from http://en.wikipedia.org/w/index.php?title=Estradiol&printable=yes.

Based on the foregoing, we reverse the rejection of claims 1, 3, 4, 10-14. 16-18, and 20-24 under § 103 over the combined teachings of Ungs, Fontana, and Grainger; and, of claims 5-7 under § 103 over the combined teachings of Ungs, Fontana, Grainger, and Pitha.

ORDER

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claims 1, 3, 4, 8, 10, 12-14, 16-18, 20 and 22-24 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Ungs, O'Brien, and Bauters is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 5-7, 11, and 21 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Ungs, O'Brien, Bauters, and Pitha is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1, 3, 4, 8, 10-14, 16-18, and 20-24 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Ungs, Fontana, and Grainger is REVERSED;

FURTHER ORDERED that the decision of the Examiner to reject claims 5-7 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Ungs, Fontana, Grainger, and Pitha is REVERSED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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